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Prognostic tools for cardiovascular disease in patients with type 2 diabetes: A systematic review and meta-analysis of C-statistics

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ABSTRACT

Background: Diabetes is associated with an increased risk for cardiovascular diseases (CVD). Risk prediction models are tools widely used to identify individuals at particularly high-risk of adverse events. Many CVD risk prediction models have been developed but their accuracy and consistency vary.
Objective: This study reviews the literature on available CVD risk prediction models specifically developed or validated in patients with diabetes and performs a meta-analysis of C-statistics to assess and compare their predictive performance.
Methods: The online databases and manual reference checks of all identified relevant publications were searched.
Results: Fifteen CVD prediction models developed for patients with diabetes and 11 models developed in a general population but later validated in diabetes patients were identified. Meta-analysis of C-statistics showed an overall pooled C-statistic of 0.67 and 0.64 for validated models developed in diabetes patients and in general populations respectively. This small difference in the C-statistic suggests that CVD risk prediction for diabetes patients depends little on the population the model was developed in ($p = 0.068$).
Conclusions: The discriminative ability of diabetes-specific CVD prediction models were modest. Improvements in the predictive ability of these models are required to understand both short and long-term risk before implementation into clinical practice.

1. Introduction

Cardiovascular diseases (CVD) are among the leading cause of death globally. According to the World Health Organization (WHO), 17.7 million people died from CVD in 2015, representing 31% of all global deaths.[1] Diabetes mellitus is a major risk factor for CVD, and individuals with diabetes are at a two to four fold higher cardiovascular risk compared to non-diabetic individuals.[2–4] Clinical practice guidelines encourage risk stratification for adults without diabetes to ensure appropriate use of therapy to reduce long-term CVD risk.[5,6] However, the routine use of risk stratification is not recommended in patients with diabetes as they are presumed to be at high risk, and there is uncertainty in the ability of currently available risk prediction models to accurately discriminate between higher and lower risk individuals within diabetic populations.[7]

A risk prediction model is a statistical tool for estimating the probability that a currently healthy individual with specific risk factors (e.g. diabetes mellitus) will develop a future condition, such as CVD, within a certain time period.[8] Prediction of outcomes (e.g. cardiovascular disease development) through modeling can provide objective estimates

Abbreviations: CVD, cardiovascular diseases; WHO, world health organization; AUC, area under the receiver operating characteristic curve; PRISMA, preferred reporting items for systematic reviews and meta-analyses; EMBASE, excerpta medica database; MEDLINE, medical literature analysis and retrieval system online; CHD, coronary heart disease; CAD, coronary artery disease; CHARMS, critical appraisal and data extraction for systematic reviews of prediction modeling studies; SE, standard error; CI, confidence interval; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; UKPDS, United Kingdom prospective diabetes study; DCS, diabetes cohort study; FDS, Fremantle diabetes study; NDR, national diabetes register; PROCAM, prospective cardiovascular Münster; JBSRC, joint British societies risk chart; SCORE, systematic coronary risk evaluation; CRM, cardio-risk manager calculator; NZGG, New Zealand guidelines group; TRIPOD, transparent reporting of a multivariable prediction model for individual prognosis or diagnosis.

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about the future course of an illness, serve as an important adjunct in clinical practice, and assist physicians in providing better care for individual patients with specified disease.[9] Accurate prediction of the outcome of interest is thus crucial for potential absolute risk reduction, providing patients with an idea of expected benefit from a treatment or intervention.

In the past decades, a number of multivariable cardiovascular risk prediction models (risk scores) have been developed in many countries to identify individuals at high risk of CVD.[10–18] These prediction models include those originally developed in individuals with diabetes[10–15] and those developed in a general population.[16–18] Though there are multiple models, little is known about which is most accurate for predicting CVD in patients with diabetes. In addition, there has been a lack of consistency in estimating risk across these different models. Model performance statistics (e.g. C-statistic or area under the receiver operating characteristic curve (AUC)) are indicators that are often used to compare different risk prediction models. To evaluate models in terms of their statistical performance, it is important to compare studies that have used the same data to generate such models.[8] These studies are rare and often not realistic. However, a pooled synthesis of performance statistics for models developed across multiple studies can be compared and assessed through a systematic review and subsequent meta-analysis. This technique can provide a comprehensive summary of the predictive ability of these models and quantitatively explore the performance statistics of the prediction models based on the reported data. Thus, the aim of our study was to identify all CVD prediction models that have been applied to patients with diabetes. We sought to characterize the populations in which these models have been derived and validated, and to assess the predictive performance and generalizability of these models to inform decisions about the selection of models for clinical implementation.

2. Material and methods

2.1. Data sources and searches

We conducted this review following a pre-specified protocol and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines[19] (Supplementary Table S1). We systematically searched MEDLINE, EMBASE and PubMed (from inception to April 12, 2016) for studies predicting the risk of CVD among patients with diabetes. We also searched the reference lists of all identified relevant publications and contacted experts in the fields of cardiovascular disease and diabetes for information about other potentially ongoing or unpublished studies. These experts were identified from the review process. We limited inclusion to studies published in English. The search strategy focused on three key elements: diabetes, risk prediction with specific names of known risk scores and cardiovascular disease. The search strategy is provided in detail in Supplemental Table S2.

2.2. Study selection

Two reviewers independently identified potentially eligible articles using a two-step process. First, an initial screen of titles and abstracts was performed. Abstract were retained if they reported data from an original study (review articles were excluded) and reported on the development and/or validation of a cardiovascular risk prediction model for patients with diabetes. We defined a CVD risk prediction model as one combining two or more independent variables to obtain estimates of the predicted risk for developing CVD. The term "CVD" here refers to a set of related key words that was used in the search process (Supplemental Table S2). At this stage, abstracts were retained when either of the reviewers believed that it should be retained or when there was uncertainty as to eligibility on the basis of title and abstract alone. Selected abstracts were later screened based on a full-text review. A broad inclusion criterion was used to provide a comprehensive systematic review of the topic. There was no restriction on study design, geographic region, or age range. Studies that developed prediction models for CVD in populations with diabetes and in the general population were included; however, models that were developed in the general population but did not validate their model in populations with diabetes were excluded. A study was included if the prediction model outcome was aggregate CVD. Models that predicted specific vascular events (such as coronary artery disease (CAD), coronary heart disease (CHD), myocardial infarction (MI), heart failure or stroke) as outcomes were excluded. A study was included if it was conducted using a real population-based cohort, while excluded if it was based solely on computer simulation. We excluded animal and biomedical studies that did not predict CVD and studies presenting a prediction model developed in patients with previous CVD or other vascular conditions (e.g., hypertensive patients). Studies that focused only on the added predictive value of a new risk factor to an existing prediction model without reporting the performance of the existing model were excluded. Studies that derived risk prediction tools other than score-type tools, such as risk charts were also excluded. Agreement between reviewers at the full-text stage was quantified using the kappa statistic. Any disagreement between reviewers was resolved by consensus.

2.3. Data extraction

Two reviewers independently extracted data using a standardized form. Data extraction from each identified study included: outcome of the prediction model, location of model development, predictors included in the model, age and gender of the study participants, number of events, duration of follow-up, modeling method used, measures of discrimination and calibration of the prediction model, and the external validation of the prediction model. For the external validation studies, a different data extraction sheet was used including specifics of the validation population, number of events, type of outcome, statistical tests and measures of discrimination and calibration of the prediction model. Study quality was assessed by each reviewer according to the CHARMS (Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies) Checklist[20] for methodological assessment of prediction research. The following items were evaluated for each study: was inclusion/exclusion criteria for study participants specified, was there non-biased selection of study participants, did the authors discuss or consider missing values/information, was there blinded assessment of the outcome, was duration of follow-up adequate, was modeling assumption satisfied, was the model externally validated, was the potential clinical utility discussed in light of study limitations.

2.4. Data analysis

The number of studies identified, included and excluded (with reason for exclusion) was summarized using the PRISMA flow diagram.[19] We defined discrimination as any assessment of the ability of the model to differentiate between subjects who will develop CVD from those who will not. The discrimination of a prediction model was most often assessed using the concordance or C-statistic (also known as the area under the receiver operating characteristic curve [AUC]). We defined calibration as any report of the agreement between predicted probabilities and observed probabilities. The calibration is assessed using goodness-of-fit tests (e.g., Hosmer–Lemeshow test), calibration slope, tabular or graphical comparisons of predicted versus observed values within groupings of predicted

risk, or calibration plots. In studies that only provided a C-statistic but no measure of its variance, the standard error (SE) and 95% confidence interval (CI) of the AUC (C-statistic) was calculated using the formula: $SE(AUC) = \sqrt{\frac{AUC[1-AUC]+[N_1-1]\times[AUC/(2-AUC)-AUC^2]+[N_2-1]\times[2AUC^2/(1+AUC)-AUC^2]}{(N_1\times N_2)}}$, where N_1=the number of patients with CVD and N_2 = the number of patients without CVD and the upper 95% CI = AUC + [1.96 × SE (AUC)], and lower 95% CI = AUC − [1.96 × SE(AUC)].[21] The summary statistic from the individual studies was the C-statistics or AUC. We grouped studies based on whether they were developed for predicting the risk of CVD in diabetic populations or in the general population but externally validated in a diabetic population. We used random effects meta-analysis to obtain the pooled weighted average C-statistic with 95% CIs for common groups of models using the DerSimonian and Laird method.[22] Heterogeneity was assessed using the Cochran Q and the I^2 statistics and was explored using meta-regression and stratified analyses according to study characteristics (specifically sample size, duration of follow-up, number of variables included within the prediction models, and geographic location). Small study effects were examined using funnel plots and Begg's test. All statistical analyses were performed using Stata version 13.1 (Stata Corp, College Station, TX) using the metan, metareg, metabias, and metafunnel commands.

3. Results

Our electronic search retrieved 21,479 citations and grey literature search retrieved an additional 113 potentially relevant citations. After removing duplicates and reviewing titles and abstracts, 165 studies remained for full text screening; the main reason for exclusion was irrelevance to our study objective. After examining the full text articles, 39 studies remained (reasons for exclusion are stated in Fig. 1), describing 26 models predicting CVD in patients with diabetes.

Among these models, 15 models were specifically developed in populations with diabetes and 11 models were initially developed in the general population and later validated in populations with diabetes. Of those models developed within populations with diabetes, 7 were externally validated by 17 studies in 16 different populations with diabetes. Six models were not validated externally. Eleven models initially developed in general populations were externally validated by 31 studies in 22 different distinct populations with diabetes, of which 8 models had single validation studies and 3 models had multiple validation studies (validated by 23 studies). The Framingham risk score (different versions) was the most validated risk score (validated by 23 studies). Fig. 1, describes the systematic selection process of studies presenting a CVD prediction model applicable to diabetes patients. Agreement

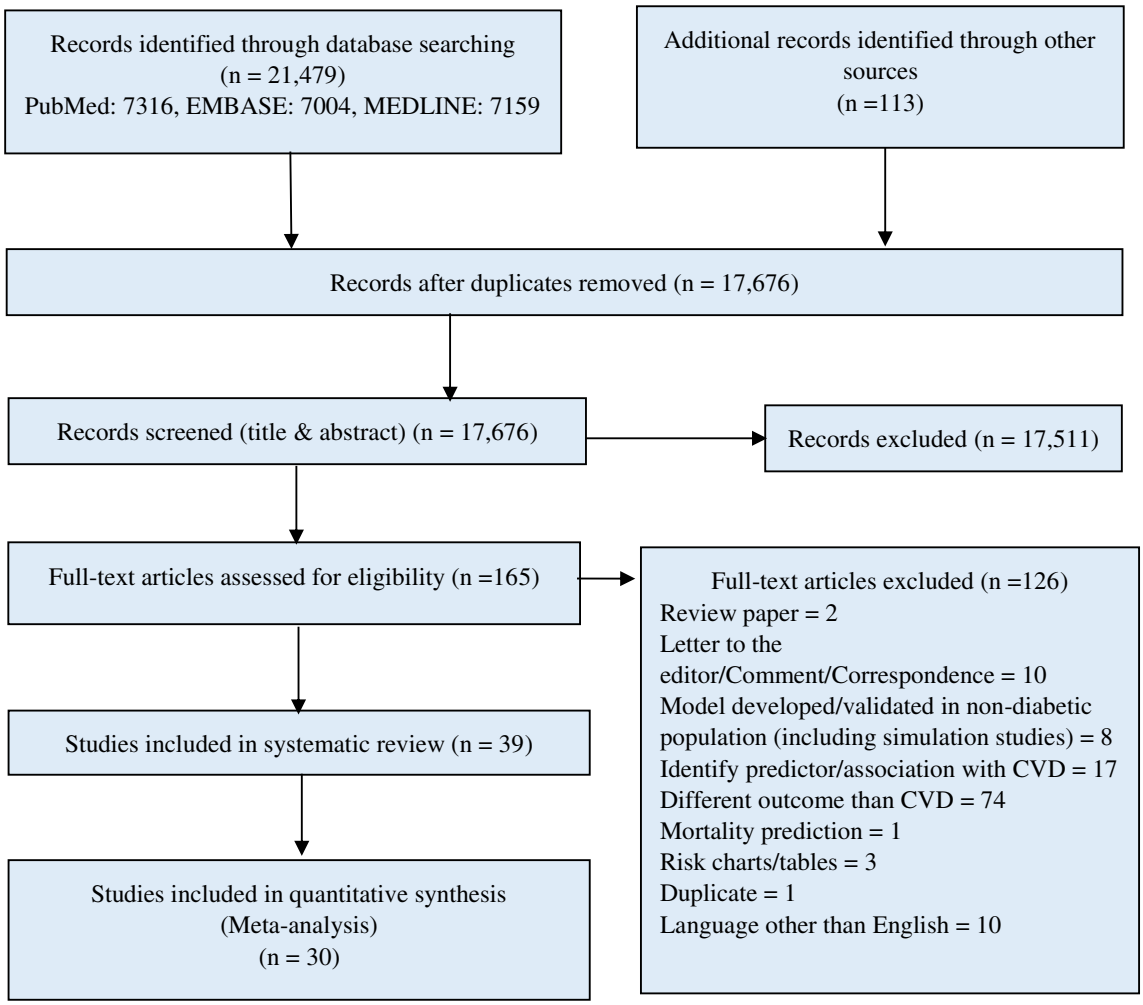

Fig. 1. PRISMA diagram for systematic review of studies presenting cardiovascular disease (CVD) prediction model developed or validated in individuals with diabetes.

Table 1
Characteristics of cardiovascular prediction models specifically developed for diabetes patients.

Study	Location	Outcome	Number of Predictors	Events(n)/total participants(N)	Duration of follow-up	Modeling method	Calibration	Discrimination	External validation
Brownrigg et al. (2014)[26]	England	CVD events (non-fatal myocardial infarction, coronary revascularisation, congestive cardiac failure, transient ischaemic attack and stroke)	6 (age, systolic blood pressure, smoking status, LDL-C and HDL-C and peripheral neuropathy (PN))	399/13043	Total 2.5 years	Probability Weighted Cox Regression	Chi square = 121.2, $p < 0.001$	C-statistic = 0.661 [0.636–0.686] (with (PN))	No
Khalili et al. (2012)[27]	Iran	CVD events (definite myocardial infarction (MI), probable MI, unstable angina, angiographic-proven coronary heart disease (CHD), stroke, death from CVD)	4 (body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), and waist-to height ratio (WHtR)	188/1010	Median follow-up 8.4 years	Cox Proportional Hazard Model	Not Reported	C-statistic = 0.64 [0.58–0.70] (for diabetic men with WHR, model 2) and C-statistic = 0.70 [0.65–0.75] (for diabetic women with WHR, model 2)	No
Cederholm et al. (2008) (NDR)[11]	Sweden	Fatal or nonfatal CVD (coronary heart disease (CHD) or stroke, whichever came first)	9 (A1C, age at onset of diabetes, diabetes duration, sex, BMI, smoking, systolic blood pressure, antihypertensive drugs and lipid-reducing drugs)	1482/11646	Mean follow-up 5.64 years	Cox Regression	HL test: Chi-square = 4.29 ($P = 0.83$) and the ratio of observed to predicted survival rates = 0.999. Excellent calibration	C-statistic = 0.70 [0.68–0.72, calculated]	Yes
Looker et al. (2015)[28]	Five cohorts from Europe	CVD (acute CHD or an ischaemic stroke)	14 (age, sex, smoking, systolic and diastolic blood pressure, LDL-C, HDL-C, triacylglycerol, diabetes duration, HbA1C, BMI, height, (eGFR), cohort, and current medication (including antihypertensive agents, aspirin, lipid lowering agents and insulin therapy)) + 6 Biomarkers (NT-proBNP apoCIII hsTnT IL-6 sRAGE IL-15)	1123/2310	Median Follow up 3.2 years for cases and 6.5 years for controls	Forward selection using logistic regression	Not Reported	AUROC = 0.72 [0.70–0.74, calculated] (Full clinical covariate set plus forward selection biomarkers)	No
Piniés et al. (2014)[29]	Spain	Fatal and non-fatal CHD and CVD	5 (Age, the ratio of non-HDL- to HDL-cholesterol, HbA1c, systolic blood pressure and smoking)	CHD: 118/704; CVD: 192/659	Mean follow-up of 8 years and a median of 10 years.	Cox proportional model	HL test: $p = 0.988$ (2-year), $p = 0.066$ (5-year), $p < 0.01$ (10-year)	Uno's C-statistic = 0.77 [0.67, 0.88] (2-year), = 0.66 [0.60, 0.72] (5-year) and = 0.68 [0.63, 0.72] (10-year)	No
Zethelius et al. (2011)[14]	Sweden	Fatal/nonfatal CVD (the composite of CHD or stroke)	12 (Onset age of diabetes, diabetes duration, total-cholesterol-to-HDL--cholesterol ratio, HbA1c, systolic BP, BMI, males sex, smoker, microalbuminuria, macroalbuminuria, atrial fibrillation, previous CVD)	2488/24288	Mean follow-up of 4.8 years	Cox proportional hazard model	HL Chi-square = 0.13 (p = 0.9) (derivation); HL Chi-square = 10.7 ($p = 0.2$) (validation)	C-statistic = 0.71 [0.70–0.72, calculated]	No
Elley et al. (2010) (DCS)[13]	New Zealand	Time to first recorded fatal or nonfatal CVD event (ischemic heart disease,	9 (age at diagnosis, diabetes duration, sex, systolic blood pressure,	6479/36127	Median follow-up 3.9 years	Cox Proportional Hazards Regression	Comparison of observed number of	C-statistic = 0.68 [0.67–0.70]	Yes

(continued on next page)

Table 1 *(continued)*

Study	Location	Outcome	Number of Predictors	Events(n)/total participants(N)	Duration of follow-up	Modeling method	Calibration	Discrimination	External validation
		cerebrovascular accident/transient ischemic attack, or peripheral arterial disease) and CHD	smoking status, total cholesterol–to–HDL ratio, ethnicity, glycated hemoglobin (A1C), and urine albumin-to-creatinine ratio)			Model	people with events within pre specified risk groups with the number predicted by the models. Value not reported		
Svensson et al. (2013)[30]	Sweden	Fatal or non-fatal CVD, fatal or non-fatal CHD, all cause Mortality	9 (age, TC/HDL, diabetes duration, HbAlc, BMI, Systolic BP, Triglycerides, smoking status, gender)	6490/66065	Mean follow-up 5.7 years	Cox Proportional Hazards Regression	Not Reported	C-statistic = 0.77 [0.75–0.79] (eGFR according to MDRD) and C-statistic = 0.73 [0.71–0.75] (eGFR according to CKD-EPI)	No
Prado et al. (2015)[25]	Spain	CVD (morbidity and mortality)	7 (gender, age, hypertension, renal failure, insulin, admission due to cardiovascular reasons and walking habit)	39/112	Mean follow-up 2.3 ± 1.6 years	Cox Multivariate Regression Model.	Not Reported	C-statistic = 0.734 [0.64–0.83, calculated]	No
Davis et al. (2010) (Fremantle)[12]	Australia	CVD (hospitalization with myocardial infarction or stroke, and death from cardiac or cerebrovascular causes or sudden death).	7 (age, sex, prior CVD, ln (urinary albumin: creatinine ratio), lnHbA1c, ln(high density lipoprotein-cholesterol), Southern European ethnic background and Aboriginality)	185/1240	Mean follow-up 4.5 years	Cox Proportional Hazards Model	HL C ^-test. Development study: $p = 0.74$, Validation study: $p = 0.85$	Development study: AUC = 0.80 [0.76–0.84, calculated], $P < 0.001$; Validation study: AUC = 0.84 [0.76–0.91], P < 0.001	Yes
Price et al. (2014)[31]	Scotland	All CV events (fatal and non-fatal MI, angina, fatal IHD, fatal and non-fatal stroke and TIA)	18 (Age, sex, baseline CVD status, duration, diabetes treatment, lipid-lowering drugs, BP-lowering drugs, smoking status, BMI, sBP, dBP, HbA1c, HDL-cholesterol, total cholesterol, eGFR, microalbuminuria and social status + NT-proBNP) (Model D)	All CV Events (n) = 112/Total participants (N) = 1066	4 years	Cox proportional hazards model	Not Reported	C-statistic = 0.748 [0.691, 0.805] (Model D)	No
Ofstad et al. (2013)[24]	Norway	Death or first CV event (myocardial infarction, stroke or hospitalization for unstable angina pectoris)	11 (Conventional risk factors: age, gender, known CVD, diastolic blood pressure, microalbuminuria, serum levels of HDL-cholesterol and creatinine); and (Novel risk markers: IL-6, log ActivinA, E/Em, pathol recovery loop)	36/132	8.6 ± 2.1 years	Cox Proportional Hazard Model	Not Reported	C-statistic: Standard (STD) model: 0.794; STD + IL-6 model: 0.913; STD + log ActivinA model: 0.859; STD + IL-6 + log ActivinA model: 0.923; STD + E/Em + pathol recovery loop model: 0.891	No
Kengne et al. (2011) (ADVANCE)[10]	20 Countries (Asia, Australasia, Europe and Canada)	CVD (fatal or non-fatal myocardial infarction or stroke or cardiovascular death)	10 (Age at diagnosis, Known duration of diabetes, Sex, Pulse pressure, Treated hypertension, Atrial fibrillation, Retinopathy, HbA1c, Log of urinary albumin/creatinine ratio and Non-HDL cholesterol at baseline)	473/7168	4.5 years	Cox Regression Model	HL test: $p = 0.76$ ((ADVANCE cohort), HL test: $p = 0.032$ (DIABHYCAR cohort)	AUC = 0.702 [0.676–0.728] (ADVANCE cohort), AUC = 0.685 [0.646–0.724] (DIABHYCAR cohort)	Yes

CV, Cardiovascular; CVD, cardiovascular disease; CHD, coronary heart disease, MI, myocardial infarction; HL, Hosmer–Lemeshow.

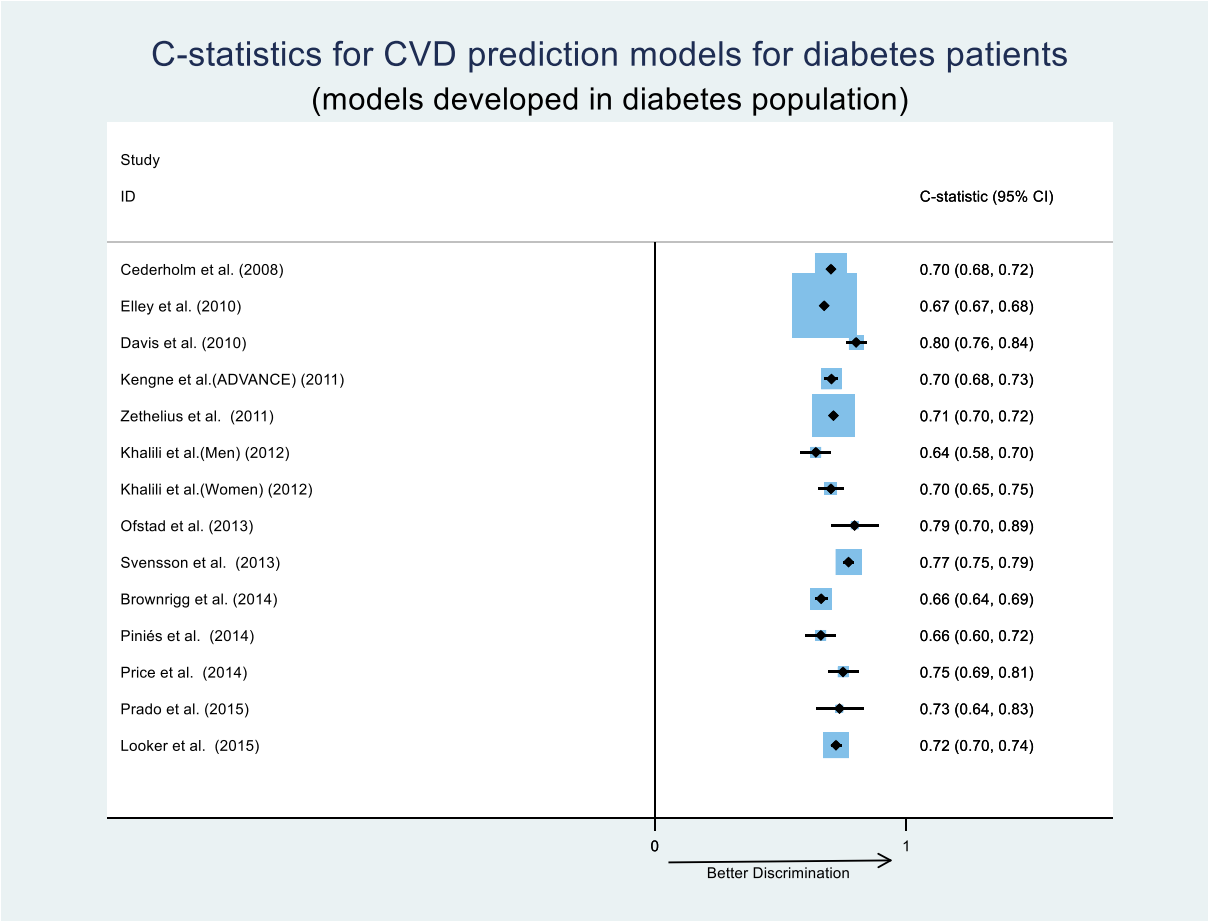

Fig. 2. Forest plot of C-statistics, with 95% confidence intervals (CIs) of risk prediction models for CVD developed in diabetes population.

between reviewers on the final articles eligible for inclusion was good ($\kappa = 0.82$).

3.1. CVD prediction models developed in diabetes population

In total, 15 risk prediction models for CVD were found specifically developed in patients with diabetes. Among these 15 models, the outcome was CHD in one model[15] and the rest were CVD. However, the model with CHD as the outcome was later validated in other populations where its outcome was renamed as CVD. In addition, we initially excluded one model[23] because data was only partially available (through abstract only). However, this model was later validated by another study. Consequently, information from these 2 models[15,23] was incorporated within the validation studies section below and information from the remaining 13 models were considered in this section. A summary of the characteristics of the prediction models developed in this patient population are described in Table 1. The number of participants ranged from 112 to 66,065 in the model development phase. The majority of studies reported composite outcomes. Duration of follow-up (total/median/mean) ranged from 2.3 to 10 years with six models following patients for >5 years (defined as long follow-up) and seven models for <5 years (short follow-up). The number of predictors included in the prediction models ranged from 4 to 18 with an average of 9 predictors per model. Several predictors were common to multiple models with the most common predictors including age, sex, duration of diagnosed diabetes, systolic blood pressure, High-density lipoprotein (HDL), HbA1c, and smoking status. The majority of these models were developed using Cox proportional hazard modeling techniques except for one where logistic regression was used. Only seven of these models were externally validated following their development and eight were never validated in an external population.

Calibration of the prediction models was reported in 7 studies with the Hosmer-Lemeshow test being the most commonly reported measure with varying level of calibration. Discrimination assessed using the C-statistic (or AUC) was reported in all of the prediction models with values ranging from 0.64 to 0.92. A pooled random effects model found a large amount of heterogeneity in the discriminative performance of these models (median C-statistic of 0.71 [range, 0.64–0.80; $I^2 = 91.1\%$; Cochran Q-statistic $p < 0.001$]; Fig. 2). Sample size (small (≤median of 2310) versus large (> median), $p = 0.45$), follow-up time (short versus long, $p = 0.85$), variables included in the model (few (< average 9) versus many (≥average), $p = 0.42$) and geographic location (Europe versus other, $p = 0.63$), were not significant sources of heterogeneity based on meta-regression. The discriminative ability of the model by Davis et al.[12] was highest (C-statistic = 0.80), however when novel biomarkers were added to conventional risk factors, the model by Ofstad et al.[24] showed the highest discriminative ability (C-statistic = 0.923). The funnel plot and Begg's test ($p = 0.826$) suggested the absence of small study effects, with no correlation between studies of smaller cohorts reporting higher C-statistics (Supplemental Fig. S1).

The quality of the studies where models were developed in populations with diabetes is summarized in Table 2. Almost all of the

Table 2
Study quality assessment of CVD prediction models developed in diabetes patients.

Study	Inclusion/exclusion criteria specified	Non biased selection	Missing value/loss to follow-up considered	Modeling assumptions satisfied	Model validation	Outcome assessed without knowledge of the candidate predictors (i.e., blinded)	Duration of follow up long enough	Potential clinical use of the model discussed	Study limitations discussed
Brownrigg et al. (2014)[26]	Yes	No	No	No	No	Not clear	No	Yes	Yes
Khalili et al. (2012)[27]	Yes	No	No	Yes	No	Not clear	Yes	Yes	Yes
Cederholm et al. (2008)[11]	Yes	Not clear	No	Yes	No	Not clear	Yes	Yes	Yes
Looker et al. (2015)[28]	Yes	Not clear	Yes	Not clear	No	Not clear	No	Yes	Yes
Piniés et al. (2014)[29]	Yes	Not clear	Not clear	Yes	No	Not clear	Yes	No	Yes
Zethelius et al. (2011)[14]	Yes	Not clear	No	Yes	No	Not clear	No	Yes	Yes
Elley et al. (2010)[13]	Not clear	Not clear	Yes	Yes	Yes	Not clear	No	No	No
Svensson et al. (2013)[30]	Yes	Not clear	Yes	Yes	No	Not clear	Yes	Yes	Yes
Prado et al. (2015)[25]	Yes	Yes	Yes	No	No	Not clear	No	Yes	Yes
Davis et al. (2010)[12]	Not clear	Not clear	No	Yes	Yes	Not clear	No	No	No
Price et al. (2014)[31]	Yes	Not clear	Not clear	No	No	Not clear	No	No	Yes
Ofstad et al. (2013)[24]	Yes	Not clear	Yes	Yes	No	Not clear	Yes	Yes	Yes
Kengne et al. (2011)[10]	Yes	Yes	Not clear	Not clear	Yes	Not clear	No	Yes	Yes

studies specified inclusion/exclusion criteria. Non-biased selection of study participants was clear for only 2 studies (Prado et al.[25] and Kengne et al.[10]). Handling of missing data was reported in 5 (38%) of the studies, modeling assumption was satisfied by 8 (62%) studies, model validation was performed in 3 (23%) studies. None of the studies mentioned whether outcomes were assessed without knowledge of the candidate predictors. Duration of follow-up was >5 years in 5 models (38%) and most of the studies reported the clinical use of the models and the study limitations.

3.2. External validation of CVD prediction models developed in diabetes populations

Among the CVD prediction models that were developed in populations with diabetes, seven of them were externally validated in independent cohorts (Table 3) and five of them had multiple validations. (Fig. 3). In total, there were 17 validation studies of these seven models in 16 different diabetic populations. Leeuw et al.[32] validated four of these seven models in three different diabetes populations. The United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine by Stevens et al.[15] was the most externally validated model with 6 studies reporting its performance on 5724 patients. Those models that had multiple validations and provided enough information to estimate the variance of the C-statistics were considered for meta-analysis. Table 4 provides a summary of the pooled C-statistics for different external validated models. Pooled C-statistics were quite similar and ranged from 0.66 to 0.70. A high amount of heterogeneity was observed in the pooled C-statistics for UKPDS[15] and FDS[12] models while almost no heterogeneity was observed in other models. Most of the external validation studies reported the calibration of their model in independent cohorts. The models by Zethelius et al.[14] and Coleman et al.[23] were validated once with a C-statistic of 0.72 each. Overall pooled C-statistics for all of the models that had multiple validations was 0.67 (95% CI, 0.66–0.69) with modest heterogeneity between studies ($I^2 = 58.9\%$; Cochran Q statistic $p < 0.001$).

3.3. External validation of CVD prediction models developed in the general population

Eleven risk prediction models for CVD originally developed in the general population were externally validated in diabetes population by 31 studies in 22 independent cohorts (Table 5). Six studies validated more than one risk model in the same population. Three of these eleven models had multiple validations (Fig. 4) and eight models had a single validation. The Framingham risk score by D'Agostino et al.[18] was the most frequently externally validated model with 13 studies reporting its performance in different diabetes cohorts. In 13 external validation studies, 33,336 patients were included with considerable variation in number of patients per study. Similar to the models developed in diabetes populations, pooled C-statistics were close to those developed in general populations (Table 4). A high degree of heterogeneity was observed in C-statistics in all models except the model by Wilson et al.[17] Most of the external validation studies did not report the calibration of their model in independent cohorts. Separate

Table 3
Characteristics of external validation studies of CVD prediction models developed in diabetes population.

Study name	Number of studies	Validation study	Location	Outcome	Events (n)/total participants (N)	Calibration	Discrimination
Kengne et al. (2011) (ADVANCE)[10]	2	Kengne et al. (2011)[10]	16 Countries	CVD	183/1836	HL test: p = 0.032	C-statistic = 0.69 [0.646–0.724]
		Leeuw et al. (2015)[32]	The Netherlands, Germany	CVD	EPIC-N: 91/453; EPIC-Potsdam: 73/1174; SMART: 58/584	EPIC-NL: Chi-Square = 14.56 ($p = 0.307$); EPIC-Postdam: Chi-Square = 9.93 ($p = 0.714$); SMART: Chi-Square = 9.97 ($p = 0.426$)	EPIC-NL: C-statistic = 0.62 [0.54–0.7]; EPIC-Postdam: C-statistic = 0.67 [0.59–0.75]; SMART: C-statistic = 0.68 [0.58–0.77]
Cederholm et al.(2008) (NDR)[11]	2	Cederholm et al. (2008)[11]	Sweden	Fatal or nonfatal CVD (coronary heart disease or stroke, whichever came first)	261/3068	Good calibration: ratio of observed CVD rate to predicted risk 0.96	C-statistic = 0.69 [0.65–0.73, calculated]
		Leeuw et al. (2015)[32]	The Netherlands, Germany	CVD	EPIC-N: 91/453; EPIC-Potsdam: 73/1174; SMART: 58/584	EPIC-NL: Chi-Square = 8.99 ($p = 0.715$); EPIC-Postdam: Chi-Square = 10.29 ($p = 0.683$); SMART: Chi-Square = 20.19 ($p = 0.059$)	EPIC-NL: C-statistic = 0.64 [0.56–0.72]; EPIC-Postdam: C-statistic = 0.67 [0.59–0.74]; SMART: C-statistic = 0.64 [0.54–0.74]
Davis et al. (2010) (Fremantle)[12]	2	Davis et al. (2010)[12]	Australia	CVD	24/180	HL C ^-test: $p = 0.85$	C-statistic = 0.84 [0.76–0.91]
		Leeuw et al. (2015)[32]	The Netherlands, Germany	CVD	EPIC-N: 91/453; EPIC-Potsdam: 73/1174; SMART: 58/584	EPIC-NL: Chi-Square = 16.73 ($p = 0.166$); EPIC-Postdam: Chi-Square = 8.12 ($p = 0.885$); SMART: Chi-Square = 11.18 ($p = 0.423$)	EPIC-NL: C-statistic = 0.58 [0.50–0.66]; EPIC-Postdam: C-statistic = 0.68 [0.60–0.76]; SMART: C-statistic = 0.69 [0.59–0.79]
Elley et al. (2010) (DCS)[13]	3	Elley et al. (2010)[13]	South New Zealand	CVD	2507/12626	Good calibration	C-statistic = 0.68 [0.67–0.70]
		Leeuw et al. (2015)[32]	The Netherlands, Germany	CVD	EPIC-N: 91/453; EPIC-Potsdam: 73/1174; SMART: 58/584	EPIC-NL: Chi-square = 6.06 ($p = 0.759$); EPIC-Postdam: Chi-Square = 6.50 ($p = 0.960$); SMART: Chi-Square = 7.69 ($p = 0.779$)	EPIC-NL: C-statistic = 0.63 [0.55–0.71]; EPIC-Postdam: C-statistic = 0.66 [0.59–0.74]; SMART: C-statistic = 0.67 [0.57–0.77]
		Robinson et al. (2012)[33]	New Zealand	CVD (hospital admission or death from ischaemic heart disease, cerebrovascular disease or peripheral vascular disease)	235/1829	HL test: $p < 0.001$ (DCS-A); HL test: $p = 0.001$ (DCS-B)	C-statistic = 0.678 [0.642–0.714] (DCS-A); C-statistic = 0.684 [0.648–0.720] (DCS-B)
Zethelius et al. (2011)[14]	1	Zethelius et al. (2011)[14]	Sweden	Fatal/nonfatal CVD (the composite of CHD or stroke)	522/4906	P/O ratio = 0.97 and $\chi^2 = 10.7$ ($p = 0.2$). Adequate calibration	C-statistic = 0.72 [0.69–0.75, calculated]
Stevens et al. (2001) UKPDS Risk Engine (UKPDS 56)[15]	6	Stephens et al. (2004)[34]	UK	CVD and CHD	358 (CVD), 269 (CHD)/798	The ratio of overall observed events/predicted events is 1.20 for CVD and 1.6 for CHD, Poor calibration ($P < 0.001$)	C-statistic = 0.74 [0.70–0.78] (CVD); C-statistic = 0.76 [0.72–0.80] (CHD)
		Simpson et al. (2011)[35]	Canada	CVD	Events (n) NR/$N = 223$	NR	NR
		Pellegrini et al. (2011)[36]	Italy	Coronary events (fatal or non-fatal MI and sudden death)	230/1532	NR	AUROC = 0.68 [0.63–0.73]
		van Dieren et al. (2011)[37]	The Netherlands, Germany	CHD (myocardial infarction and ischaemic heart disease) and CVD (myocardial infarction, ischaemic heart disease or stroke)	CHD: 55/1622; CVD: 78/1622	CHD: HL Chi-square = 77.4 ($p < 0.001$); CVD: HL Chi-square = 48.1 ($p < 0.001$)	CHD: C-statistic = 0.65* [0.50–0.80]; CVD: C-statistic = 0.65* [0.53–0.79]
		Lutgers et al. (2009)[38]	The Netherlands	Fatal + Non-fatal CV Events	119/973	NR	AUC = 0.58 [0.52–0.64, calculated]
		Elkeles et al. (2008)[39]	UK	CHD CVD	CHD:56/566 CVD:66/576	NR	CHD: AUC ROC = 0.67 [0.60, 0.75] CVD: AUC ROC = 0.63 [0.56, 0.71]
Coleman et al. (2007) UKPDS risk engine, version 3[23]	1	Simmons et al. (2009)[40]	UK	CVD	69/272	Goodness-of-fit test ($p = 0.67$), Good calibration	aROC = 0.72 [0.65–0.78]

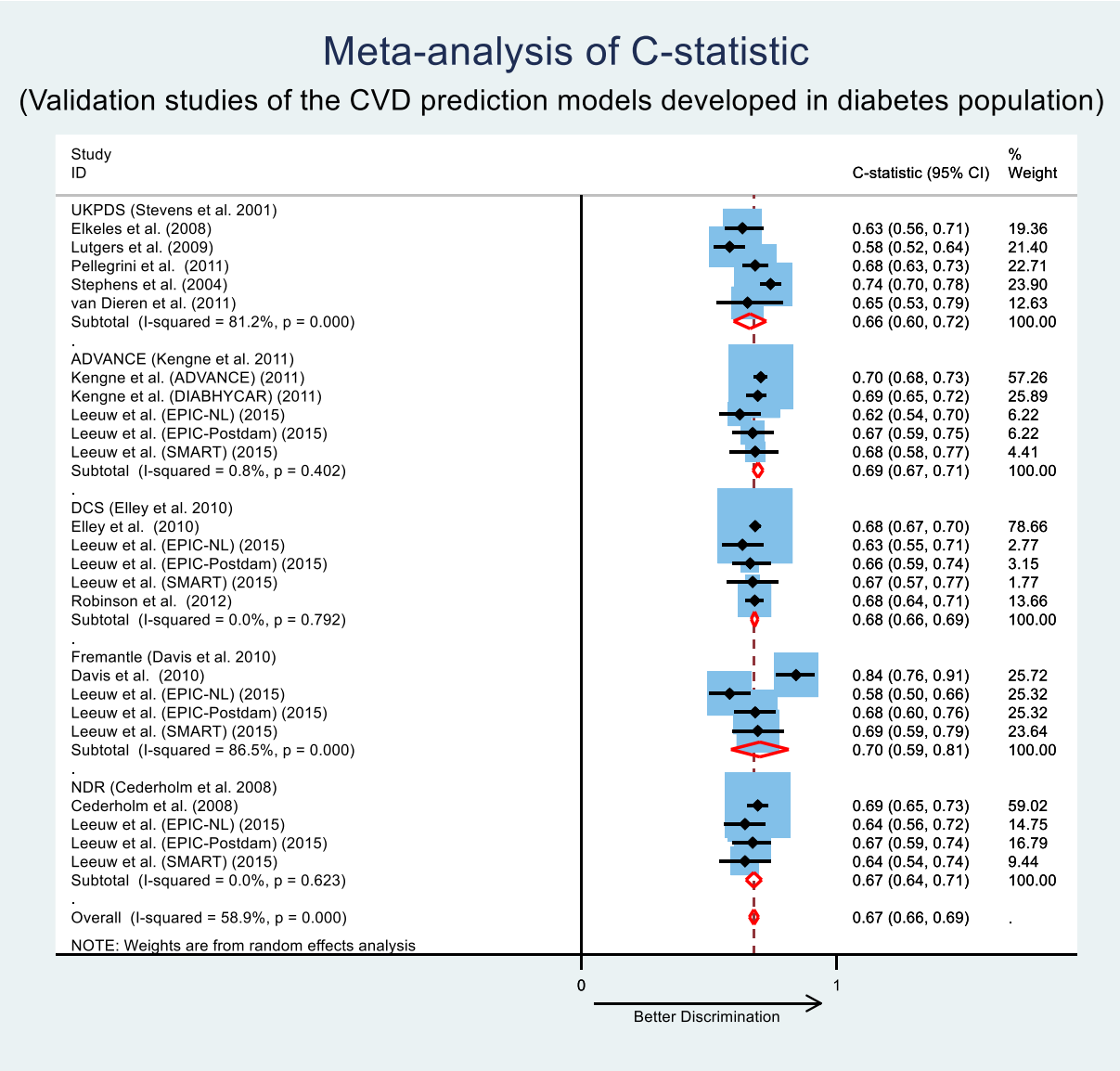

Fig. 3. Forest plot of C-statistics, with 95% confidence intervals (CIs), of CVD prediction models developed in diabetes population that are externally validated in two or more independent cohorts. Validation studies are stratified and identified by the name of the first author of the derivation study, with each external validation study identified below by the validation study's first author name.

models by Palmieri et al. (CUORE),[41] Menotti et al. (Riscard 2002),[42] Assmann et al. (PROCAM),[43] Wood et al. (Joint British Societies Risk Chart, JBSRC),[44] Hingorani et al. (CRM),[45] Conroy et al. (SCORE),[46] Balkau et al. (DECODE),[47] Mann et al. (NZGG-modified Framingham CVD equation)[48] were each validated in 1 external cohort. These separate models were externally validated by 4 studies in 4 independent cohorts with sample sizes ranging from 423 to 3898 and C-statistics ranging from 0.59 to 0.80. Overall pooled C-statistics for the models that had multiple validations was 0.64 (95% CI, 0.62–0.66) with significant heterogeneity (I^2 = 72.4%; Cochran Q statistic

Table 4
Pooled C-statistics for the external validated CVD prediction models developed in both diabetes and general population.

Model	Pooled C-statistic in validation studies with 95% CI
External validated (two or more) models developed in diabetes population	
UKPDS Risk Engine[15]	0.66 [0.60–0.72]
DCS Risk Prediction Model[13]	0.68 [0.66–0.69]
ADVANCE Risk Engine[10]	0.69 [0.67–0.71]
FDS Risk Equation[12]	0.70 [0.59–0.81]
NDR Risk Equation[11]	0.67 [0.64–0.71]
External validated (two or more) models developed in general population	
Framingham Risk Score (D'Agostino et al.)[18]	0.64 [0.61–0.66]
Framingham Risk Score (Anderson et al.)[16]	0.65 [0.61–0.68]
Framingham Risk Score (Wilson et al.)[17]	0.67 [0.62–0.71]

Table 5
Characteristics of external validation studies of CVD prediction models developed in general population.

Study name	Number of studies	Validation study	Location	Outcome	Events (n)/total participants (N)	Calibration	Discrimination
Anderson et al. (1991) (Framingham)[16]	7	Kengne et al. (2010)[49]	20 countries	Major CVD	1003/7502	HL Chi Square = 489 ($p < 0.0001$) HL Chi Square = 480.7 ($p < 0.0001$)*	C-statistic = 0.62 [0.60–0.64, calculated] C-statistic = 0.64*
		Kengne et al. (2011)[10]	16 countries	CVD	183/1836	NR	AUC = 0.65 [0.603–0.689]
		Coleman et al. (2007)[50]	UK	Fatal CVD and Fatal CHD	Events (n) NR/ 3898	Underestimated CVD event rate by 32%	C-statistic = 0.76
		Guzder et al. (2005)[51]	England	Primary CVD and CHD events	Events (n) = 98 (CVD), 60 (CHD)/428	CVD: HL Chi Square = 32.8 ($P < 0.001$), CHD: HL Chi Square = 19.8 ($P = 0.011$)	C-statistic = 0.673 [0.612–0.734]
		Metcalf et al. (2008)[52]	New Zealand	CVD	Events (n) NR/423	NR	NR
		Game et al. (2001)[53]	England	CHD CVD	Events (n) NR/906	NR	NR
		Bernard et al. (2005)[54]	Not Reported	CVD	34/229	NR	ROC = 0.72 [0.62–0.82, calculated]
Wilson et al. (1998) (Framingham)[17]	3	Pellegrini et al. (2011)[36]	Italy	Coronary events (fatal or non-fatal MI and sudden death)	230/1532	NR	AUROC = 0.68 [0.62–0.73]
		Yoshida et al. (2012)[55]	Japan	CVD	85/783	NR	ROC = 0.645 [0.58–0.71]
		Damkondwar et al. (2012)[56]	India	CVD	NR/1248	NR	NR
D'Agostino et al. (2008) (Framingham)[18]	13	Kengne et al. (2010)[49]	20 Countries	Major CVD	1003/7502	HL Chi Square = 621.1 ($p < 0.0001$) HL Chi Square = 649.9 ($p < 0.0001$)*	C-statistic = 0.63 [0.61–0.65,calculated], C-statistic = 0.65*
		Simmons et al. (2009)[40]	UK	CVD	69/272	Goodness- of -fit test: $p = 0.02$	aROC = 0.73 [0.66–0.78]
		Kengne et al. (2011)[10]	16 Countries	CVD	183/1836	NR	AUC = 0.64 [0.596–0.680]
		Echouffo-Tcheugui et al. (2008)[57]	England	Primary CVD event	Events (n) NR/683	Absolute Risk Reduction 8% with no additive effect.	NR
		Jiao et al. (2014)[58]	Hong Kong	CVD	12 (RAMP-DM), 31 (Control Group)/1072 (RAMP-DM Group), 1072 (Control Group)	NR	NR
		Looker et al. (2015)[28]	5 Cohorts from Europe	CVD (acute CHD or an ischaemic stroke)	1123/2310	NR	AUROC = 0.59 [0.57–0.61, calculated]
		García et al. (2014)[59]	Argentina	CVD, CHD and Stroke	NR/293	NR	NR
		Irie et al. (2013)[60]	Japan	CVD	34/287	NR	AUC = 0.60 [0.49–0.70]
		Katakami et al. (2012)[61]	Japan	Cardiovascular events which is composite of any CHD event (myocardial infarction, angina, and CHD death) and any ischemic stroke (fatal and nonfatal ischemic stroke)	20/85	NR	ROC = 0.60 [0.40–0.78]
		Katakami et al. (2014)[62]	Japan	CVD	113/1040	NR	AUC = 0.60 [0.54–0.67]
		Al-Lawati et al. (2012)[63]	Oman	CVD	Events (n) NR/1110	NR	NR
		Ruijter et al. (2013)[64]	17 cohorts worldwide	CVD	684/4220	NR	C-statistic = 0.671 [0.649–0.693]

(continued on next page)

Table 5 *(continued)*

Study name	Number of studies	Validation study	Location	Outcome	Events (n)/total participants (N)	Calibration	Discrimination
		Elley et al. (2010)[13]	New Zealand	CVD	2507/12626	NR	C-statistic = 0.63 [0.62–0.65]
Palmieri et al. (2003) (CUORE)[41]	1	Pellegrini et al. (2011)[36]	Italy	CVD	228/1532	Risk underestimated (O/E: 1.43, confidence limits: 1.25–1.62).	C-statistic = 0.64 [0.6–0.67]
Menotti et al. (2002) (Riscard)[42]	1	Pellegrini et al. (2011)[36]	Italy	CVD	228/1532	Risk better estimated (O/E: 1.08, 95% CI: 0.83–1.40)	C-statistic = 0.59 [0.52–0.67]
Assmann et al. (2002) (PROCAM)[43]	1	Stephens et al. (2004)[34]	UK	CVD and CHD	358 (CVD), 269 (CHD)/798	The ratio of overall observed risk/predicted risk is 2.79. Poor calibration ($P < 0.001$).	C-statistic = 0.67 [0.62–0.73]
Wood et al. (1998) (JBSRC)[44]	1	Stephens et al. (2004)[34]	UK	CVD and CHD	358 (CVD), 269 (CHD)/798	Poor calibration ($P < 0.001$)	C-statistic = 0.80 [0.75–0.85]
Hingorani et al. (1999) (CRM)[45]	1	Stephens et al. (2004)[34]	UK	CVD and CHD	358 (CVD), 269 (CHD)/798	The ratio of overall observed events/predicted events is 2.30 for CVD. Poor calibration ($P < 0.001$).	C-statistic = 0.76 [0.72–0.79]
Conroy et al. (2003) (SCORE)[46]	1	Coleman et al. (2007)[50]	UK	Fatal CVD and Fatal CHD	Events (n) NR/3898	Overestimated 10-year fatal CVD event rate by 18% (Observed event rate 7.4% vs Absolute Risk (AR) 8.7%)	C-statistic = 0.77
Balkau et al. (2004) (DECODE)[47]	1	Coleman et al. (2007)[50]	UK	Fatal CVD and Fatal CHD	Events (n) NR/Total $N = 3898$	Acceptable CVD event rate estimate (Observed event rate 7.4% vs Absolute Risk (AR) 6.6%) and underestimated CHD event rate by 11%	C-statistic = 0.67
Mann et al. (2003) (NZGG-modified Framingham CVD equation)[48]	1	Metcalf et al. (2008)[52]	New Zealand	CVD	Events (n) NR/$N = 423$	NR	NR

NR, not reported; CVD, cardiovascular disease; CHD, coronary heart disease, MI, myocardial infarction; HL, Hosmer–Lemeshow.

$p < 0.001$). Models that were developed in diabetes populations for predicting CVD in diabetes patients did not exhibit significantly higher C-statistics than models developed in the general population (meta-regression $p = 0.068$).

4. Discussion

This review provides an overview of all CVD prediction models that are specifically developed for, or validated in patients with diabetes to calculate future cardiovascular risk. Overall, we found that less than half of the prediction models that were specifically designed for patients with diabetes had been externally validated. A greater proportion of models developed in a general population had been validated in populations with diabetes (the most notable prediction model was the Framingham risk score with 23 validation studies of its different versions), many of these models had a single validation and as a result, performance of the models was difficult to assess. Collectively, our findings suggest that additional validation studies on the performance of these prediction models in adults with diabetes are needed. Furthermore, none of the models that have been validated in more than one dataset demonstrated consistently outstanding performance in terms of discrimination. The discriminative ability of both diabetes-specific CVD prediction models and prediction models developed in the general population were modest with C-statistics often below 0.70.[65] Despite the fact that CVD prediction models developed in the general population do not account for diabetes-specific risk factors, there is little evidence to suggest that using risk scores developed in a population with diabetes will help to estimate CVD risk among patients with diabetes more accurately than those developed in the general population.

Meta-analyses of the C– statistic suggest that there is significant between-study heterogeneity of the models developed in the general population that were externally validated in two or more diabetes populations. While sources of heterogeneity were unexplained, it may be that differences in patient characteristics across study cohorts may explain some of this observed heterogeneity. However, geographic location of the patients (Europe versus other) was not identified as a significant source of heterogeneity in meta-regression. Generally, heterogeneity was attenuated in studies of the models developed in populations with diabetes although there was considerable variation in model quality and methodology used to develop them.

Our findings suggest that from the large list of published models, only a few well-validated models are available for CVD prediction in patients with diabetes. Study quality assessment also showed that many of the models developed in patients with diabetes failed to meet three key criteria: non-biased selection, reporting of model validation and blinded outcome assessment. These findings highlight the lack of standard reporting in this area of literature. This may be due to lack of guidelines for standards of reporting for risk prediction studies during that time. Authors often reported different aspects of the prediction models and in varying ways, which created difficulty for data collection and standardization within this review. Recently, new guidelines such as the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD)[66] have been

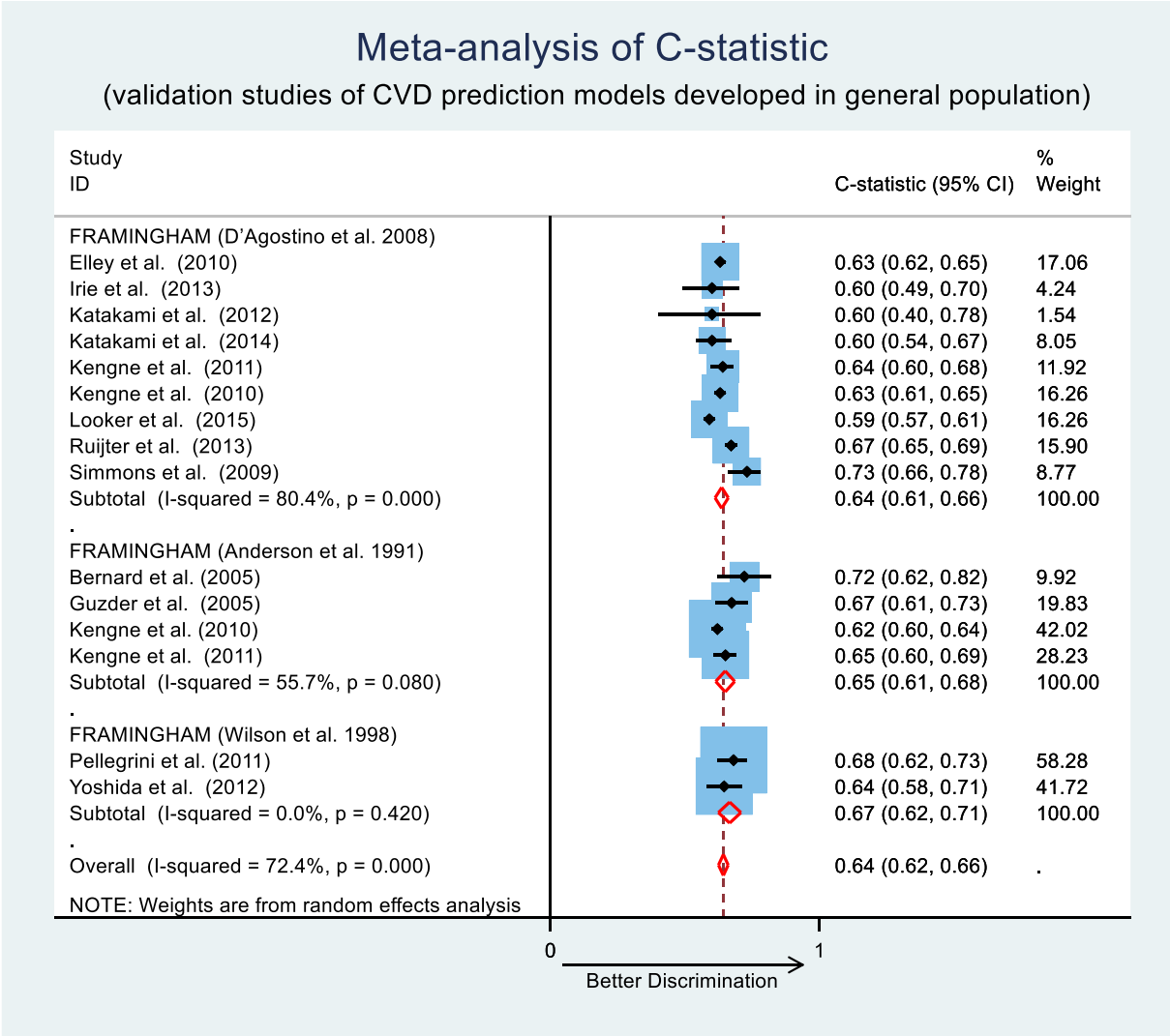

Fig. 4. Forest plot of C-statistics, with 95% confidence intervals (CIs), of CVD prediction models developed in general population that are externally validated in two or more independent diabetes cohorts. Validation studies are stratified and identified by the name of the first author of the derivation study, with each external validation study identified below by the validation study's first author name.

introduced to assist authors and may improve reporting in future studies in this area.

A major strength of this study is the comprehensiveness of the systematic review, which included a search of three different databases and extensive use of reference lists, decreasing the likelihood of missing relevant studies. Further, to our knowledge this is the first study to perform a meta-analysis and a comprehensive assessment of study quality on CVD prediction models in diabetes patients. Nevertheless, there are several limitations to our systematic review and meta-analysis. We only considered studies that used population-based models and did not consider models that were computer simulation-based such as UKPDS OM2,[67] CDC-RTI,[68] Archimedes,[69] Cardiff Diabetes Model,[70] and ECHO-T2DM.[71] While the inclusion of these simulation-based models could potentially improve the generalizability of our findings, it would have also increased the amount of between study heterogeneity that exists within these models making the pooled estimates more difficult to interpret. Further, we only considered models that reported the aggregate outcome of cardiovascular disease (CVD) and excluded those that reported individual macrovascular event types (i.e. MI, IHD, and stroke) that constitutes CVD. However, we believe this to be an important area for future work to understand the differential predictive ability of these models if we had looked at each macrovascular event type separately. We were only able to make detailed comparisons of model performance on the basis of the C-statistic, which might be insensitive to differences in the ability of models to accurately risk-stratify patients into clinically meaningful risk groups.[72] Specifically, performing a meta-analysis of additional calibration measures (e.g. E/O ratios) along with C-statistics could provide a more comprehensive summary of the performance of these models. The CHARMS evaluation framework used for study quality assessment in this systematic review has some limitations and may not be applicable to cross compare models that use entirely different approaches of model development (e.g. CDC-RTI[68]). Thus, study quality should be interpreted with caution. Regardless, the results of our systematic review suggest that there is no overall difference between the discrimination of models developed in diabetes population and the general population for predicting risk of CVD in diabetes patients. Models, particularly those that have not been validated or validated once may require further external validation in a new population in which they will be used with or

without recalibration or model updating to better understand the comparative performance of these models.

5. Conclusions

We have identified a considerable number of models for predicting CVD in diabetes patients and have comprehensively compared these models. Overall, it is difficult to recommend one model over another as none of the models showed outstanding discriminative performance, and unfortunately no single model appears to perform consistently well. Most of the models were developed and validated with a follow-up time of <5 years. Also not all models accounted for diabetes duration as a risk factor in their model development, which makes it difficult to interpret the long-term risk of CVD. This is important considering the fact that diabetes is a chronic condition where both short and long-term risk are of interest from a patient and provider perspective. Risk stratification is an important clinical activity that helps tailor and individualize therapy, and is typically encouraged by clinical practice guidelines in the management of other cardiovascular risk factors. The use of a prediction model in the clinical setting is to help clinicians make a quick and accurate assessment of their patients' risk of CVD, and provide a transparent platform to communicate this risk to the patient. While these models may have potential to improve care planning in the future, additional work is required to truly understand both short and long-term CVD risk within this population as well as the identification of additional factors that may help improve prediction in subsequent models. The inability to reliably use risk stratification in the care of diabetes leads to all patients being aggressively treated to reduce risk. Research is therefore needed to identify new risk factors with high associated relative risk that add large predictive ability over and above currently used factors to improve the currently available prediction models.

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